Version with Markings to Show Changes Made

Novel Metalloproteinase Inhibitors

1. Field of the Invention

The present invention relates to novel compounds which inhibit metalloproteinases, intermediates for the production thereof and processes for producing the same. More preferably, the present invention relates to novel compounds, having advantageous biological properties such as excellent oral bioavailability, which inhibit vertebrate matrix metalloproteinases (MMPs) and/or tumor necrosis factor-α (TNF-α)-converting enzymes (TNF-α convertases), intermediates for the production thereof and processes for producing the same.

[Background of the Invention] 2 Description of the Related Art

Among metalloproteinases, matrix metalloproteinases ("MMPs") are a family of endoproteinases containing zinc. The MMPs are involved in the degradation of extracellular matrices in connective tissues. Up until now, it has been known that the MMPs include dozens of MMP species. The expression of these enzymes is strictly controlled in healthy persons; however, abnormal increases of MMPs are observed in Alzheimer's disease, Parkinson's disease, pancreatitis, ulcerative colitis, aphthous ulcer, autoimmune diseases (including chronic rheumatoid arthritis, Crohn's disease, and anemia associated with autoimmune diseases), osteoarthritis, periodontal diseases and disorders, corneal ulcer, uveitis, a variety of bullae (including congenital epidermolysis bullosa, acquired epidermolysis bullosa, porphyria cutanea tarda (PCT), pemphigoid, and pemphigus vulgaris), refractory dermal ulcers (including bedsore, dermal ulcer in radiotherapeutic patients, dermal ulcer in diabetic patients, and dermal ulcer in patients suffering from arteriosclerosis obliterans), osteoporosis, Behcet's disease, aberrant angiogenesis (accompanying tumor growth, and including lymphoma, ovary cancer, and tumor metastasis and invasion), cachexia,

too heavy a load on patients but also have serious drawbacks in view of readiness and convenience for cases where patients take the drug by themselves. Furthermore, most of diseases and disorders associated with the degradation of tissues often turn to chronic, thereby necessitating the continued use of drugs lasting for a long time. In such cases, oral administration is thought to be the most suitable route.

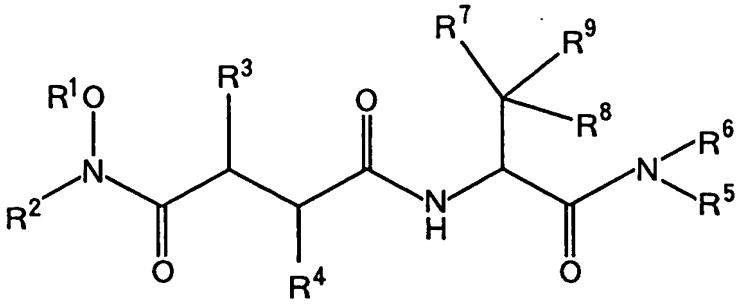
However, it is hard to orally administer the prior art compounds in such manners. Therefore, they are still unsatisfactory therapeutic agents at this stage.

Summary of the Invention

The present inventors have conducted an extensive research on hydroxamic acid-based derivatives with high inhibitory activity against MMPs with a view to improving and increasing their utilizability. As a result, the present inventors have succeeded in (1) producing novel hydroxamic acid derivatives which not only have unexpectedly high inhibitory activity against MMPs but also exert (i) potent bioavailability, including the property of being significantly well absorbed by oral routes, and (ii) excellent biological activity, superior to those of the prior art compounds, and (2) providing the present invention.

Thus, the present invention provides

(1) a compound having the following formula (I):



(I)

methyl;

(35) a process for producing a compound of the formula (III) according to the above (34) or a pharmaceutically acceptable salt or solvate thereof;

(36) a pharmaceutical or veterinary composition which comprises (a) an effective amount of at least a member selected from the group consisting of a compound of the formula (III) according to the above (34) and a pharmaceutically or veterinarily acceptable salt or solvate thereof, and (b) a pharmaceutically or veterinarily acceptable excipient or carrier;

(37) an inhibitor of the destruction of bones comprising an effective amount of at least a member selected from the group consisting of a compound of the formula (III) according to the above (34) and a pharmaceutically or veterinarily acceptable salt or solvate thereof;

(38) an agent for the prophylaxis and/or treatment of osteoporosis comprising an effective amount of at least a member selected from the group consisting of a compound of the formula (III) according to the above (34) and a pharmaceutically or veterinarily acceptable salt or solvate thereof; and

(39) use of a compound of the formula (III) according to the above (34) for prophylactically and/or therapeutically treating diseases and/or disorders associated with the degradation of bone tissues.

The above objects and other objects, features, advantages, and aspects of the present invention are readily apparent to those skilled in the art from the following disclosures. It should be understood, however, that the detailed description of the specification including the following ~~best~~

description

~~modes~~ of ~~carrying out~~ the invention, examples, etc. is illustrating preferred embodiments of the present invention and given only for explanation thereof. It will become apparent to the skilled in the art that a great number of variations and/or alterations (or modifications) of this invention may be made based on knowledge from the disclosure in the following parts and other parts of the specification without departing from the spirit and scope thereof as disclosed herein. All of the patent publications and reference documents cited herein for illustrative purposes are hereby incorporated by reference into the present disclosure.

The term "and/or" used herein means the presence of both (1) a jointly connecting relation and (2) a selectively connecting relation. For example, in the case of "prophylactically and/or therapeutically", it is used in such a sense that said expression covers both (1) "prophylactically and therapeutically" and (2) "prophylactically or therapeutically". In other cases, the term "and/or" is used in the same sense that it covers both (1) a jointly connecting relation and (2) a selectively connecting relation as well.

Detailed Description of ~~Best Modes of Carrying out~~ the Invention

As used herein for R^1, R^3, R^4, R^5, R^6, R^7, R^8 and R^{10} in the compounds given above, specifically the compounds (I), (IV), and (VI), the term "unsubstituted or optionally substituted alkyl" refers to a straight chain or branched alkyl moiety, preferably having from 1 to 20 carbon atoms, more preferably from 1 to 12 carbon atoms, and most preferably from 1 to 9 carbon atoms, which can optionally be unsubstituted or substituted with one or more substituents which can be selected from the group given hereinbelow, including for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, hexyl, heptyl, and octyl.

more hetero atoms (which are identical or different) selected from nitrogen, oxygen, sulfur, etc., which can optionally be unsubstituted or substituted with one or more substituents (said substituent is selected from those given hereinbelow). Said unsubstituted or optionally substituted heterocyclic group includes for example, radicals having a 5-, 6- or 7-membered heterocyclic ring. Representatives of the "heterocyclic ring" include imidazole, pyrazole, imidazoline, imidazolidine, pyridine, pyrimidine, benzimidazole, quinazoline, pteridine, purine, 1,3-azepine, aziridine, azetidine, pyrrole, pyrrolidine, tetrahydropyridine, piperidine, azepine, indole, quinoline, isoquinoline, morpholine, piperazine, etc.

When R^5 and R^6 taken together with the nitrogen atom to which they are attached form an "unsubstituted or optionally substituted heterocyclic group", said term "unsubstituted or optionally substituted heterocyclic group" refers to a saturated ~~suturated~~ or unsaturated nitrogen-containing radical, being monocyclic or having multiple condensed rings, such as a bicyclic radical, wherein said heterocycle includes, for example, aziridine, azetidine, pyrrole, pyrrolidine, pyridine, tetrahydropyridine, piperidine, azepine, indole, quinoline, isoquinoline, morpholine, piperazine, etc.

As used herein for the term "hydroxy-protecting group" in connection with R^1 and the term "protected hydroxy" in connection with R^{11} and R^{14} in the compounds (I) and (IV), suitable protecting groups are those known to artisans in the organic synthesis fields, for example, selected from those which have been employed in the technical fields including peptide synthesis, penicillin synthesis, cephalosporin synthesis, sugar synthesis, and the like. Said "hydroxy-protecting groups" and said "protecting groups" include those removable by treatment with water, those removable by hydrogenolysis, those removable with Lewis catalysts such as $AlCl_3$, those removable with zinc/acetic acid, those removable with thiourea, those removable with acids or

Biological Example 1

Assay for inhibition of collagenase

The efficacy of compounds of the present invention to act as inhibitors of human fibroblast collagenase was determined by the procedure of Y. Murawaki et al. (Journal of Hepatology, 18, p.328-334, 1993), compared with a reference compound.

Procollagenase was activated by incubation with 2 mM 4-aminophenylmercuric acetate (APMA) at 35°C for 2 hours. The inhibition was assayed using, as a substrate, fluorescein-labeled bovine type I collagen. To a solution of the substrate (0.5 mg/ml) in a 50 mM Tris-HCl buffer, pH 7.5, containing 0.4M aqueous sodium chloride and 10 mM aqueous potassium chloride was added the activated collagenase. The resultant solution was incubated at 35°C for 2 hours. The digestion of the substrate with the enzyme was stopped by addition of 80 mM o-phenanthroline, followed by addition of a porcine elastase solution formed by dissolving 25μ g/ml porcine elastase in the aforementioned Tris-HCl buffer. The mixture was incubated at 37°C for 10 minutes. To the resulting solution was added 70% ethanol, and a 170 mM Tris-HCl buffer, pH 9.5, containing 0.67M aqueous sodium chloride. Undigested substrates were precipitated by centrifugation at 3000 x g for 20 minutes. The supernatant was collected and the fluorescence was read using an excitation wavelength of 495 nm and an emission wavelength of 520 nm. The inhibitory potency of the compounds was calculated. IC_{50} represents the concentration of each test compound required for 50% inhibition of cleavage of substrates by the enzyme alone. The resulting assay data for representative examples are shown in Table 1, compared with the reference compound. The Reference Compound No. 1 is N-[4-(N-hydroxyamino)-2(R)-n-propyloxymethyl-3(S)-isopropyl-thiomethylsuccinyl]-O-methyl-L-tyrosine-N-methylamide which is synthesized according to the procedure of USP No. 5,442,110.

Biological Example 2

Assay for inhibition of stromelysin

The efficacy of compounds of the present invention to act as inhibitors of human fibroblast stromelysin was determined by the procedure of Twining (Anal. Biochem., 143, p.30, 1984), compared with a reference compound.

Prostromelysin was activated by incubation with 20μ g/ml human plasmin at 37°C for 2 hours, and the reaction was stopped by addition of 2.8 mg/ml aqueous diisopropyl fluorophosphate. The inhibition was assayed using, as a substrate, fluorescein-labeled casein. To a solution of the substrate (1 mg/ml) in a 50 mM Tris-HCl buffer, pH 7.8, containing 10mM aqueous calcium chloride was added the activated stromelysin. The resultant solution was incubated at 37°C for 2 hours. The digestion of the substrate with the enzyme was stopped by addition of 5% trichloroacetic acid. Undigested substrates were precipitated by centrifugation at 3000 x g for 20 minutes. The supernatant was collected, followd by additon of a 0.5M Tris-HCl buffer, pH 8.5. The fluorescence was read using an excitation wavelength of 495 nm and an emission wavelength of 520 nm. The inhibitory potency of the compounds was calculated. IC_{50} represents the concentration of each test compound ~~requited~~ required for 50% inhibition of cleavage of substrates by the enzyme alone. The resulting assay data for representative examples are shown in Table 2, compared with the reference compound.

All isomers of the compounds of the present invention having the same optical configurations as the Reference Compound exert more intense inhibition than those of the Reference Compound.

The following ~~simbols~~ symbols are intended to have the meanings set forth below in the specification and the appended claims:

$N^a = N^{\alpha}$
$N^e = N^{\varepsilon}$
$N^d = N^{\delta}$
$N^g = N^{g}$
$N^w = N^{\omega}$

~~Industrial Applricability~~

The compounds provided by the present invention, for example, the compounds of the formula (I), exert potent metalloproteinase-inhibiting activity and have not only excellent inhibitory actions on MMPs and/or TNF-α convertases but also remarkably improved bioavailablity, in comparison with the prior art compounds. Accordingly, these compounds can be applied to diseases and/or disorders associated with tissue degradation, leading to unexpectedly excellent actions and effects and promising therapeutic and/or prophylactic results.

While the present invention has been described specifically in detail with reference to certain embodiments and examples thereof, it would be apparent that it is possible to practice it in other forms. In light of the disclosure, it will be understood that various modifications and variations are within the spirit and scope of the appended claims.

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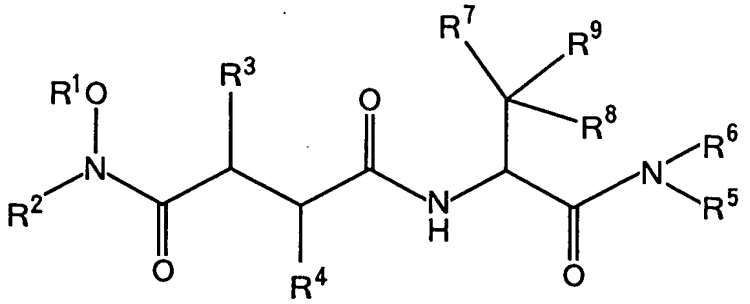
WHAT IS CLAIMED IS

1. A compound having the following formula (I):



(I)

wherein R^1 is selected from the group consisting of hydrogen, unsubstituted or optionally substituted aralkyl, silyl which may optionally have three substituents, tetrahydropyranyl, unsubstituted or optionally substituted aralkyloxycarbonyl, unsubstituted or optionally substituted alkyloxycarbonyl, unsubstituted or optionally substituted alkyl, and a hydroxy-protecting group;

R^2 is selected from the group consisting of hydrogen, unsubstituted or optionally substituted aralkyloxycarbonyl, unsubstituted or optionally substituted alkyloxycarbonyl, 9-fluorenylmethyloxycarbonyl, and an amino-protecting group;

R^3 is selected from the group consisting of hydrogen, hydroxy, unsubstituted or optionally substituted alkyl, and unsubstituted or optionally substituted aralkyl;

R^4 is selected from the group consisting of unsubstituted or optionally substituted alkyl, and unsubstituted or optionally substituted aralkyl;

R^5 and R^6, which may be identical or different, are each independently selected from the group consisting of hydrogen, unsubstituted or optionally substituted alkyl, unsubstituted or optionally substituted cycloalkyl, an unsubstituted or optionally substituted heterocyclic group, and an amino-protecting group, or R^5 and R^6 taken together

with the nitrogen atom to which they are attached form an unsubstituted or optionally substituted heterocyclic group;

R^7 is selected from the group consisting of hydrogen, hydroxy, unsubstituted or optionally substituted alkyl, and unsubstituted or optionally substituted aralkyl;

R^8 is selected from the group consisting of hydrogen, hydroxy, unsubstituted or optionally substituted alkyl, and unsubstituted or optionally substituted aralkyl; and

R^9 is selected from the group consisting of hydrogen, hydroxy, amino, and a group of the formula: -X-Y

wherein X is selected from the group consisting of unsubstituted or optionally substituted (C_1-C_6) alkylene, and unsubstituted or optionally substituted phenylene, and

Y is a group of the formula: -A-B or -B,

wherein A is selected from the group consisting of unsubstituted or optionally substituted (C_1-C_6) alkylene, oxygen, sulfur, imino, and unsubstituted or optionally substituted (C_1-C_6) alkyleneimino, and

B is selected from the group consisting of hydrogen, amino, amidino, acylimidoyl, unsubstituted or optionally substituted imidazolyl, unprotected or optionally protected bis(phosphono)methyl, and unprotected or optionally protected bis(phosphono)hydroxymethyl;

or a pharmaceutically acceptable salt or solvate thereof.

2. ~~The~~ A compound ~~according to claim 1 wherein~~ having the following formula (I): [Insert formula (I) from claim 1] Wherein R^1 and R^2 are hydrogen;

R^3 is selected from the group consisting of (C_1-C_9) alkyl, (C_3-C_7) cycloalkyl-substituted lower (C_1-C_4) alkyl, hydroxy, amino-substituted (C_1-C_6) alkyl, phenyl-lower (C_1-C_4) alkyl, guanido-substituted phenyl-lower (C_1-C_4) alkyl, amino-substituted phenyl-lower (C_1-C_4) alkyl, carboxy-substituted phenyl-lower (C_1-C_4) alkyl, carbamoyl-substituted phenyl-lower (C_1-C_4) alkyl, hydroxy-substituted phenyl-lower (C_1-C_4) alkyl, guanido-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, unprotected or optionally protected

optionally substituted benzimidoyl, bis(phosphono)methyl, tetra-lower (C_1-C_4) alkyl bis(phosphono)methyl, tri-lower (C_1-C_4) alkyl bis(phosphono)methyl, bis(phosphono)hydroxymethyl, tetrabenzyl bis(phosphono)hydroxymethyl, and lower (C_1-C_4) alkyl-substituted imidazol-3-yl, and

A is selected from the group consisting of lower (C_1-C_4) alkylene, imino, and lower (C_1-C_4) alkylene-imino;

Provided that a combination wherein R^7 is methyl, R^8 is methyl and R^9 is methyl is excluded;

or a pharmaceutically acceptable salt or solvate thereof.

3. The compound according to claim 1 or 2 wherein

R^1 and R^2 are hydrogen;

R^3 is selected from the group consisting of ~~hydroxy~~, methyl, isobutyl, aminopropyl, phenylpropyl, guanidophenylpropyl, aminophenylpropyl, hydroxyphenylpropyl, carboxyphenylpropyl, carbamoylphenylpropyl, aminomethylphenylpropyl, guanidomethylphenylpropyl, hydroxymethylphenylpropyl, aminomethylbenzyl, toluenesulfonamidomethylbenzyl, methanesulfonamidomethylbenzyl, isobutyliminomethylbenzyl, phthalimidomethylbenzyl, phenoxyethyl, aminopentyl, acetimidoyliminopentyl, isobutyliminopentyl, pyridylmethyliminopentyl, methoxycarbonylphenylpropyl, ethoxyethoxyethyl, hydroxyoctyl, butoxyethyl, iso-butyloxyethyl, morpholinopropyl, (3,4,4-trimethyl-2,5-dioxo-imidazolidin-1-yl)propyl, cyclohexylpropyl, and piperidinopropyl;

R^4 is selected from the group consisting of naphthylmethyl, phenylpropyl, isobutyl, tert-butyl, isopropyl, and hydroxyoctyl;

R^5 is selected from the group consisting of methyl, cyclopropyl, 2-(N,N-dimethylamino)ethyl, 2-carboxyethyl, 2-hydroxyethyl, 2-hydroxy-1,1-dimethylethyl, 2-hydroxy-1-methylethyl, 6,6-bis(phosphono)-6-hydroxyhexyl, tetrabenzyl 6,6-bis(phosphono)-6-hydroxyhexyl, piperidyl, and morpholinyl;

R^6 is hydrogen;

R^7 is hydrogen or methyl;

R^8 is hydrogen or methyl; and

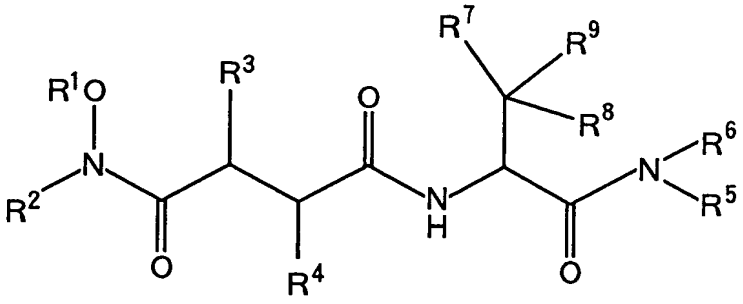
R^9 is selected from the group consisting of hydrogen, hydroxy, amino, and a group of the formula: -X-Y

wherein X is selected from the group consisting of methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, and phenylene, and

Y is a group of the formula: -A-B or -B
wherein B is selected from the group consisting of amino, amidino, acetimidoyl, propionimidoyl, benzimidoyl, bis(phosphono)methyl, tetraethyl bis(phosphono)methyl, triethyl bis(phosphono)methyl, tetramethyl bis(phosphono)-methyl, trimethyl bis(phosphono)methyl, bis(phosphono)-hydroxymethyl, tetrabenzyl bis(phosphono)hydroxymethyl, and 2-methyl-imidazol-3-yl, and

A is selected from the group consisting of imino, methyleneimino, and methylene.

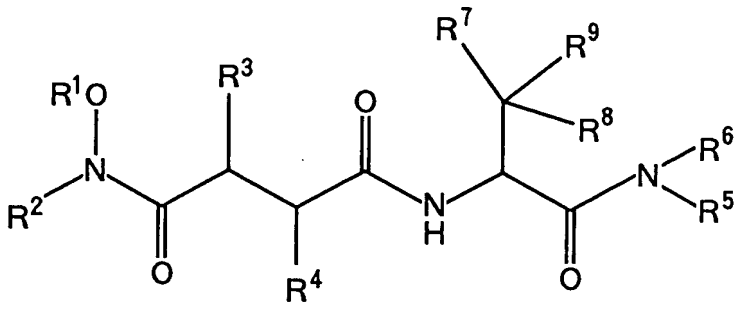
4. A pharmaceutical or veterinary composition which comprises (a) an effective amount of at least a member selected from the group consisting of a compound of the formula (I):



(I)

wherein R^1 to R^9, all have the same meanings as defined in claim 21, and a pharmaceutically or veterinarily acceptable salt or solvate thereof, and (b) a pharmaceutically or veterinarily acceptable excipient or carrier.

5. A metalloproteinase inhibitor which comprises an effective amount of at least a member selected from the group consisting of a compound of the formula (I):



(I)

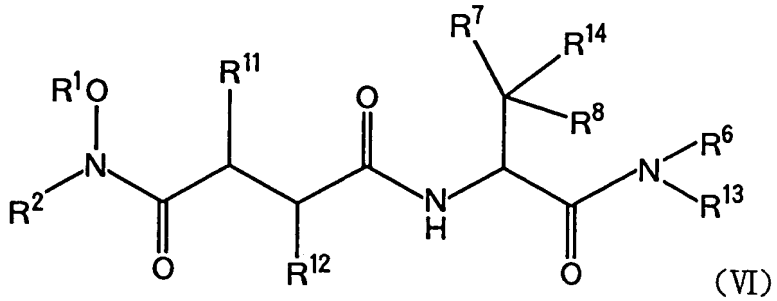
wherein R^1 to R^9, all have the same meanings as defined in claim 1, and a pharmaceutically acceptable salt or solvate thereof.

6. The inhibitor according to claim 5 wherein the metalloproteinase is selected from the group consisting of matrix metalloproteinases and the inhibitor is a kind of inhibitors of matrix metalloproteinase.

7. The inhibitor according to claim 5 wherein the metalloproteinase is selected from the group consisting of tumor necrosis factor-α (TNF-α)-converting enzymes and the inhibitor is a kind of inhibitors of TNF-α convertase.

8. ~~Use of a compound of the formula (I) according to claim 1 for~~ A method of prophylactically and/or therapeutically treating diseases and/or disorders associated with tissue degradation, comprising administering a effective amount of the compound according to claim 2

to form a compound of the formula (VI):

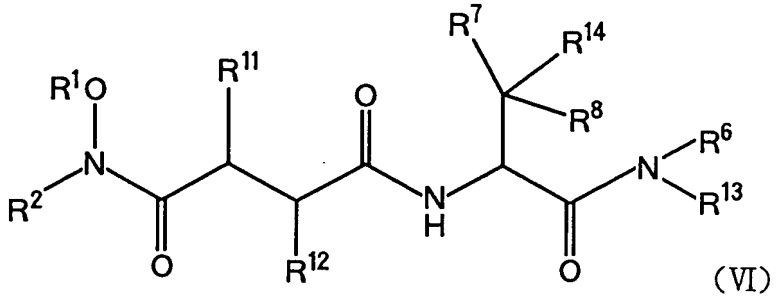


(VI)

and, if desired, optionally converting R^{11}, R^{12}, R^{13} and/or R^{14} into the target functional group(s), R^3, R^4, R^5 and/or R^9, respectively,

wherein R^1 to R^9, all have the same meanings as defined in claim 1, and R^{11} to R^{14}, all have the same meanings as defined in claim 9.

12. A compound having the following formula (VI):



(VI)

wherein R^1, R^2, and R^6 to R^8, all have the same meanings as defined in claim 2, ~~and R^{11} to R^{14}, all have the same meanings as defined in claim 9~~, [Insert paragraph A'] or a salt thereof.

Paragraph "A"

R^{11} has the same meaning as defined for R^3, or is selected from the group consisting of protected hydroxy, protected guanido-substituted phenyl-lower (C_1-C_4) alkyl, protected amino-substituted phenyl-lower (C_1-C_4) alkyl, nitro-substituted phenyl-lower (C_1-C_4) alkyl, protected amino-substituted (C_1-C_6) alkyl, nitro-substituted (C_1-C_6) alkyl, protected carboxy-substituted phenyl-lower (C_1-C_4) alkyl, protected hydroxy-substituted phenyl-lower (C_1-C_4) alkyl, protected guanido-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, protected amino-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, protected hydroxy-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, protected carboxy-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, protected hydroxy-containing (C_1-C_8) straight chain or branched alkyl, and cyano-substituted phenyl-lower (C_1-C_4) alkyl;

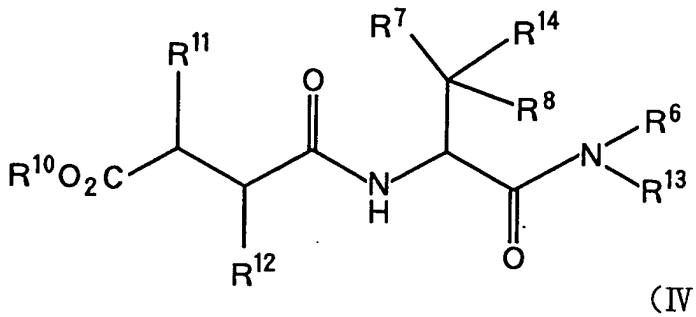
R^{12} has the same meaning as defined for R^4, or is protected hydroxy-substituted (C_1-C_8) alkyl;

R^{13} has the same meaning as defined for R^5, or is selected from the group consisting of protected carboxy-substituted lower (C_1-C_4) alkyl, protected hydroxy-substituted lower (C_1-C_4) alkyl, protected bis(phosphono)hydroxymethyl-substituted (C_1-C_{11}) alkyl, and a protected nitrogen-containing heterocyclic group; and

R^{14} has the same meaning as defined for R^9, or is selected from the group consisting of protected amino, protected hydroxy, and a group of the formula: -X-E or -X-A-E

wherein X and A, both have the same meanings as given above, and E is selected from the group consisting of nitro, cyano, amino, carboxyl, (C_1-C_{11}) hydroxyalkyl, protected amino, protected guanido, protected amidino, protected acylimidoyl, protected benzimidoyl, protected bis(phosphono)methyl, protected bis(phosphono)hydroxymethyl, and protected (C_1-C_{11}) alkyl-substituted imidazol-3-yl;

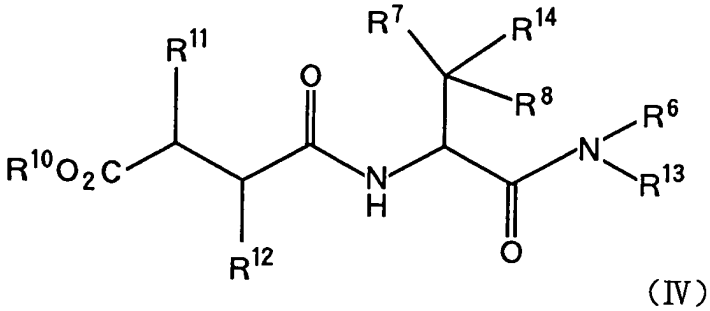
13. A compound having the following formula (IV):



(IV)

wherein R^6 to R^8, all have the same meanings as defined in claim 12, ~~and R^{10} to R^{14}, all have the same meanings as defined in claim 9,~~ [Insert paragraph "B"] or a salt thereof.

14. A process for producing a compound having the following formula (IV):



(IV)

or a salt thereof,
which comprises reacting a succinic acid derivative of the formula (II):

PARAGRAPH "B"

R^{10} is selected from the group consisting of unsubstituted or optionally substituted alkyl, unsubstituted or optionally substituted aralkyl, and a carboxy-protecting group;

R^{11} has the same meaning as defined for R^3, or is selected from the group consisting of protected hydroxy, protected guanido-substituted phenyl-lower (C_1-C_4) alkyl, protected amino-substituted phenyl-lower (C_1-C_4) alkyl, nitro-substituted phenyl-lower (C_1-C_4) alkyl, protected amino-substituted (C_1-C_6) alkyl, nitro-substituted (C_1-C_6) alkyl, protected carboxy-substituted phenyl-lower (C_1-C_4) alkyl, protected hydroxy-substituted phenyl-lower (C_1-C_4) alkyl, protected guanido-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, protected amino-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, protected hydroxy-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, protected carboxy-substituted lower (C_1-C_4) alkyl-substituted phenyl-lower (C_1-C_4) alkyl, protected hydroxy-containing (C_1-C_8) straight chain or branched alkyl, and cyano-substituted phenyl-lower (C_1-C_4) alkyl;

R^{12} has the same meaning as defined for R^4, or is protected hydroxy-substituted (C_1-C_8) alkyl;

and protected (C_1-C_{11}) alkyl-substituted imidazol-3-yl;

R^{13} has the same meaning as defined for R^5, or is selected from the group consisting of protected carboxy-substituted lower (C_1-C_4) alkyl, protected hydroxy-substituted lower (C_1-C_4) alkyl, protected bis(phosphono)hydroxymethyl-substituted (C_1-C_{11}) alkyl, and a protected nitrogen-containing heterocyclic group; and

R^{14} has the same meaning as defined for R^9, or is selected from the group consisting of protected amino, protected hydroxy, and a group of the formula: -X-E or -X-A-E

wherein X and A, both have the same meanings as given above, and E is selected from the group consisting of nitro, cyano, amino, carboxyl, (C_1-C_{11}) hydroxyalkyl, protected amino, protected guanido, protected amidino, protected acylimidoyl, protected benzimidoyl, protected